MONOCYCLIC AROMATIC AMINES
Category Justification and Testing Rationale

CAS Nos. 91-66-7, 102-27-2, 99-97-8, and 103-69-5

(Plus SIDS/ICCA chemicals 62-53-3, 121-69-7, 95-53-4, 108-44-1, and 106-49-0 for data purposes).

Monocyclic Aromatic Amines and Nitroaromatics Panel
American Chemistry Council
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Member companies in the Monocyclic Aromatic Amines and Nitroaromatics Panel are Albemarle Corporation, Bayer Corporation, Buffalo Color Corporation, and First Chemical Corporation.

I. INTRODUCTION

The Monocyclic Aromatic Amines and Nitroaromatics Panel and its member companies submit for review and public comment their test plan for monocyclic aromatic amines in the Environmental Protection Agency's High Production Volume (HPV) Challenge Program (the HPV program). The member companies are committed to making existing test data publicly available for products in this category and developing any additional screening level data needed on health and environmental effects, fate, and physiochemical properties.

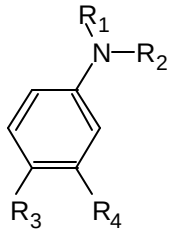
In order to minimize the use of animals in the testing of chemicals, the Panel has conducted a thorough literature search for all available data, published and unpublished. It also has performed an analysis of the adequacy of the existing data. Further, it developed a scientifically supportable category of related chemicals and used structure-activity relationship information as appropriate. No testing of whole animals is proposed; only *in vitro* genetic toxicity testing is included to develop needed screening data.

This document describes the monocyclic aromatic amines included in the HPV program and notes the related chemicals that are being sponsored through the International Council of Chemical Associations' (ICCA) testing program and the OECD SIDS program. Data on all these chemicals are included to provide justification for the proposed categories. IUCLID documents have been prepared and are included for each of these chemicals. Finally, the rationale for proposed testing is described.

II. DEVELOPMENT OF THE MONOCYCLIC AROMATIC AMINES CATEGORY

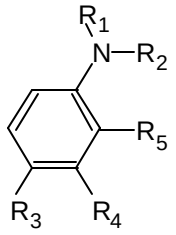
All chemicals included in the program are monocyclic aromatic amine compounds. The aromatic amines all have a single amino group and are secondary or tertiary amines with methyl or ethyl substituents on the nitrogen atom. Some of these aromatic amines also have a methyl substituent on the aromatic ring. Figure 1 gives the names, CAS numbers, and structures of the compounds in the HPV program. Other chemicals in this category are scheduled for review under the ICCA program and are undergoing or have undergone review in the OECD SIDS program. The data from these chemicals provides a more complete understanding of this category, and they are listed in Figure 2.

Figure 1. Monocyclic Aromatic Amines Included in the HPV Program



Chemical Name	CAS Number	R1	R2	R3	R4
N,N-Diethyl aniline	91-66-7	C_2H_5	C_2H_5	H	H
N,N-Dimethyl-p-toluidine	99-97-8	CH_3	CH_3	CH_3	H
N-Ethyl m-toluidine	102-27-2	C_2H_5	H	H	CH_3
N-Ethyl aniline	103-69-5	C_2H_5	H	H	H

Figure 2. Related Monocyclic Aromatic Amines



Chemical Name	CAS Number	R1	R2	R3	R4	R5	Program
o-Toluidine	95-53-4	H	H	H	H	CH_3	ICCA
p-Toluidine	106-49-0	H	H	CH_3	H	H	ICCA
m-Toluidine	108-44-1	H	H	H	CH_3	H	OECD SIDS
Aniline	62-53-3	H	H	H	H	H	OECD SIDS
N,N-Dimethyl aniline	121-69-7	CH_3	CH_3	H	H	H	OECD SIDS

Manufacturing, Use, and Exposure Information on Monocyclic Aromatic Amines

The N-alkyl substituted aromatic amines (N,N-diethyl aniline, N,N-dimethyl-p-toluidine, N-ethyl-m-toluidine, and N-ethyl aniline) are typically manufactured by reaction of aniline or a toluidine isomer with either ethanol or acetaldehyde for N-ethyl derivatives, or methanol or formaldehyde for the N-methyl compounds. The largest category of use for these chemicals is as chemical intermediates in the synthesis of a variety of organic chemicals. Because the majority of the production volume is converted to other chemicals (i.e., is used as a chemical intermediate), human and environmental exposure is limited. N,N-Diethyl aniline is used as a chemical intermediate to make dyes, pesticides, polyester resins, and pharmaceuticals. N-Ethyl-m-toluidine is an intermediate in the production of dyes and color developers for photographic films, while N-ethyl aniline is an intermediate in the production of dyes and pharmaceuticals. N-Ethyl aniline is also used as a promoter in the production of polyester resins. Two products, N,N-dimethyl-p-toluidine and N,N-diethyl aniline, are also used as cure accelerators in unsaturated polyester and epoxy vinyl resins and cyanoacrylate adhesives. In this application, they chemically reduce peroxides used as initiators of polymerization at room temperature.

Because of their use as chemical intermediates, the potential for exposure exists primarily in the workplaces of the manufacturers and their customers. The manufacturers use and recommend both personal protective equipment and engineering controls. Splash-proof chemical safety goggles, full-faceshields, or full-face respirators are recommended to protect against eye contact. Local exhaust ventilation is recommended to minimize inhalation exposure. Organic vapor cartridge respirators are recommended for use if there is a potential for exposure to vapors or mists. In case of a spill or leak, appropriate protection, which may include a respirator with supplied air, is required. Appropriate gloves, aprons, and chemical resistant clothing are used to prevent dermal contact.

Test Plan Rationale

There is a large amount of test data available for the four sponsored HPV aromatic amines and the five other related aromatic amines. These data allow the use of categories and estimation to predict effects where data are missing. The IUCLID documents enclosed for each chemical summarize the available studies. The critical studies to fulfill required HPV Challenge endpoints were chosen according to several factors, including documentation and detail, when the study was conducted, and access to a detailed publication or report. Overall, existing data has been identified for all of the HPV Challenge endpoints, however, as explained in detail below, the Panel proposes to perform low pH cell transformation assays on N-ethyl aniline and N-ethyl-m-toluidine.

Physical and Chemical Properties

The physical and chemical properties of all the chemicals in the category are summarized in Table 1 below. All 4 HPV compounds are liquids at room temperature, with relative densities ranging from 0.9625 (N-ethyl aniline) to 0.9307 (N,N-diethyl aniline). The boiling points all range from 184°C (aniline) to 221°C (N,N-dimethyl-p-toluidine). The vapor pressure range at 25°C is from 0.70 mm Hg for N,N-dimethyl aniline to an estimated value of 0.125 mm Hg for N-ethyl-m-toluidine. Water solubility data are available for 8 of the 9 compounds, and range from 36 g/l (aniline) to 0.13 g/l (N,N-diethyl aniline). The water solubility of N,N-dimethyl-p-toluidine is estimated at 0.46 g/l. The range of the log of the octanol-water partition coefficients is from 0.91 (aniline) to 3.2 (N,N-diethyl aniline). These data are sufficient to describe the properties of this category, and no further testing is proposed.

Table 1. Physical and Chemical Properties

	Aniline 62-53-3	o-Toluidine 95-53-4	p-Toluidine 106-49-0	m-Toluidine 108-44-1	N,N-Dimethyl aniline 121-69-7	N-Ethyl aniline 103-69-5	N,N-Dimethyl-p-toluidine 99-97-8	N-Ethyl-m-toluidine 102-27-2	N,N-Diethyl aniline 91-66-7
Molecular weight	93.13	107.16	107.16	107.16	121.18	121.18	135.21	135.21	149.24
Melting point (ºC)	-6.2	-16.3	43.7	-31.2	2.4	-63.5	-6.6	8.7	-38.8
Boiling point (ºC)	184.0	200.3	200.4	203.3	194.1	203.0	211	221	216.3
Density g/cc at 20º C	1.0213	0.9984	0.9619	0.9889	0.9557	0.9625	0.9366	0.9450	0.9307
Vapor pressure, mm Hg at 25º C	0.49	0.26	0.286	0.303 (Chao et al, 1990)	0.70	0.31	0.178	0.125 (est);1.00 mm at 54º C	0.136
Log P	0.91	1.4	1.39	1.4	2.28	1.92	2.81	2.66	3.17
Water solubility, g/l	36	8	11	12	1.2	2.7	0.46	1.1	0.13

= ICCA and OECD SIDS chemicals

Metabolism

Metabolism of arylamines generally proceeds through N-oxidation, hydroxylation of aromatic ring carbons, and formation of conjugates such as glucuronides, sulfates, and acetates (Kharchevnikova and Zholdakova, 1997; Cheever et al, 1980; Son et al, 1980). Ring alkyl substituents may also be oxidized to alcohols and further metabolized to acids (Son et al, 1980). N-Oxidation is an important step that can lead to the formation of metabolites that will react with cellular macromolecules (Kiese, 1963; Burstyn et al, 1991; Garner et al, 1984). The N-phenylhydroxylamines and nitrosobenzenes produced by N-oxidation are capable of binding to the heme ion in hemoglobin and causing oxidation. This reaction can produce the methemoglobinemia that is the most typical toxicity associated with aromatic amines. Aniline itself is oxidized primarily to o- and p-aminophenol. These metabolites are subsequently conjugated with glutathione to form o- and p-aminophenylmercapturic acids for urinary excretion (Radomski, 1979; Baranowska-Dutkiewicz, B, 1982; Irons et al, 1980; Williams, 1959; Parke, 1960). For three of these arylamines, the rates of both N-oxidation and N-dealkylation *in vitro* were found to occur in the order N,N-dimethyl-p-toluidine >N,N-dimethyl aniline > N,N-diethyl aniline (Seto and Guengerich, 1993). N-ethyl aniline has also been found to be metabolized *in vitro* by N-oxidation, N-dealkylation, and ring hydroxylation (Appel et al, 1965; Seto and Guengerich, 1993). N-Dealkylation of methyl groups proceeds more rapidly than that of ethyl groups (Seto and Guengerich, 1993; Gorrod and Patterson, 1983). The most common metabolic reaction for the toluidines is ring hydroxylation. o-Toluidine undergoes hydroxylation in the para position, as well as a lesser amount of N-acetylation, and conjugation with sulfates and glucuronides (Cheever et al, 1980; Son et al, 1980). p-Toluidine is hydroxylated in the ortho position, while m-toluidine is converted to a mixture of the ortho and para-hydroxylated metabolites; these derivatives are also subsequently conjugated. (Cheever et al, 1980). While metabolism studies of N-ethyl-m-toluidine are not available, N-dealkylation and ring hydroxylation are expected based on these related chemicals. The metabolism of the eight compounds that have been studied is typical of monocyclic aromatic amines. Typical metabolic reactions are diagrammed in Figure 3.

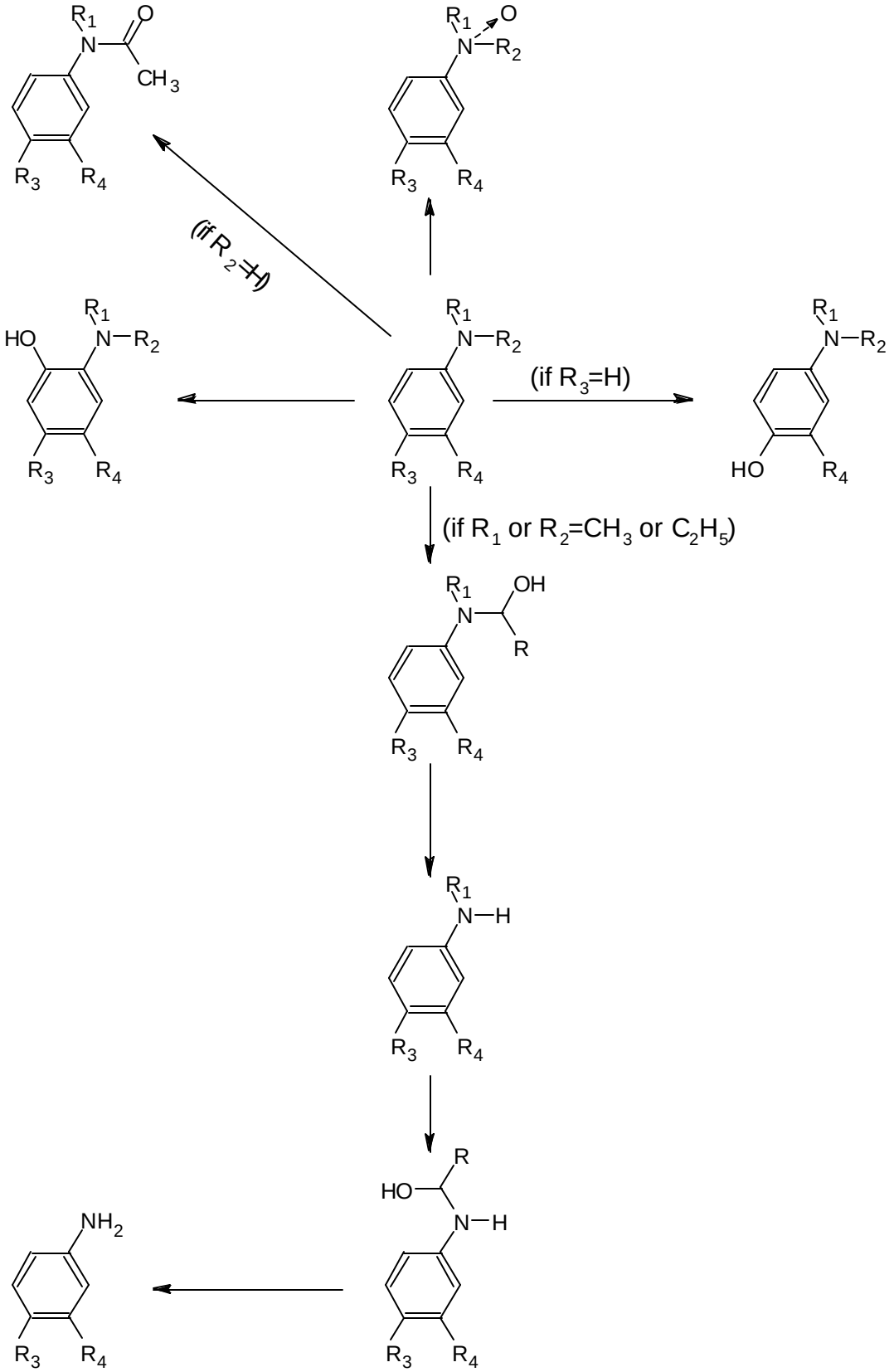
Fate

If released into water, biodegradation will be a major removal process. A short acclimation period generally enhances biodegradation of monocyclic aromatic amines. Biodegradation has been studied for three of the four HPV compounds and for five other chemicals in the category. Conflicting results have been published regarding the ready biodegradability of N-ethyl aniline. However, this chemical is inherently biodegradable. Likewise, N,N-diethylaniline was readily biodegradable by one test protocol and not readily biodegradable by another. N-Ethyl-m-toluidine was not readily biodegradable. Based on the other members of the category, N-ethyl-m-toluidine is expected to be ultimately biodegradable. Aniline, N,N-dimethyl aniline, m-toluidine, p-toluidine, and o-toluidine have all been found to be readily biodegradable, although N,N-dimethyl aniline and m-toluidine had mixed results for this endpoint. N,N-Dimethyl-p-toluidine has not been tested for biodegradation. Based on biodegradation results for these chemicals, N,N-dimethyl-p-toluidine is expected to biodegrade after acclimation. Adsorption to sediments is predicted to be low for all these aromatic amines, but the protonated forms of these bases will bind more strongly. In surface waters, photodegradation is expected to occur at a moderate to rapid rate for all four compounds. Aniline photodegradation was measured and found to occur at a moderate rate; photodegradation of N,N-dimethyl aniline occurred at a moderate to slow rate. Evaporation may also contribute to loss from water, and will be followed by photodegradation in the atmosphere. N-Ethyl aniline, aniline, o-toluidine, and p-toluidine degrade slowly in pure water in the absence of sunlight. Many aromatic amines will readily react with organic constituents in natural waters. None of the four HPV compounds is likely to bioaccumulate in aquatic organisms, based on their octanol-water partition coefficients. Lack of bioaccumulation has been demonstrated for N,N-dimethyl aniline, N,N-diethyl aniline, aniline and o-toluidine. If released into soil, leaching and reaction with organic constituents are expected to be major removal processes. Binding to soil is predicted to be low to moderate, and as for sediments, binding will vary with pH. Evaporation from dry soil is expected to be low. There are sufficient data for monocyclic aromatic amines to characterize the fate of these chemicals, and no further testing is proposed.

Aquatic Toxicity

In most acute toxicity tests, the four compounds were harmful to fish (96-hr LC_{50}>10≤100 mg/L). N-ethyl aniline was toxic (96-hr LC_{50}>1≤10 mg/L) to one species, however. N-ethyl aniline was harmful to algae, but N,N-diethyl aniline was toxic. Related chemicals in the category were not harmful to algae (N,N-dimethyl aniline), harmful (aniline, o-toluidine, and m-toluidine), or toxic (o-toluidine and p-toluidine). N,N-dimethyl-p-toluidine and N-ethyl-m-toluidine have not been tested for algal toxicity, and their algal toxicity was calculated using EPIWIN v. 3.05. Both of these compounds are predicted to be harmful to algae. N-ethyl aniline was harmful to Daphnia, as was o-toluidine in several studies, while N,N-dimethyl aniline and N,N-diethyl aniline were toxic. Aniline and m-toluidine were very toxic to Daphnia (48-hr LC_{50}≤1 mg/L); o-toluidine was also very toxic in one study. p-Toluidine was toxic to a salt water invertebrate, Mysid shrimp. The toxicity to Daphnia of N,N-dimethyl-p-toluidine and N-ethyl-m-toluidine was calculated, and both compounds were predicted to be harmful. There is a large amount of data available on chemicals in this category, and no further testing is proposed.

Figure 3. Some Typical Metabolic Reactions of the Category



Mammalian Acute Toxicity

All four of the HPV aromatic amines have been tested for acute toxicity. Three of the four compounds are considered harmful by single oral doses, as the rat oral LD_{50}'s are >500 and $\leq$2000 mg/kg. The N-ethyl substituted chemicals appear to be slightly more toxic than the N-methyl substituted group in acute oral studies, and N-ethyl aniline is considered toxic by the oral route (LD_{50}>50 and $\leq$500 mg/kg). The rabbit dermal LD_{50}'s for three compounds are all >2000 mg/kg, which is not considered harmful by single dermal applications. N,N-Diethyl aniline is considered toxic by the dermal route, with a rabbit LD_{50} of >468<935 mg/kg. Systemic toxicity was not evident after dermal application of the toluidines, N,N-dimethyl-p-toluidine and N-ethyl-m-toluidine. N-ethyl aniline, N,N-diethyl aniline, N-ethyl-m-toluidine, and N,N-dimethyl-p-toluidine are all classified as toxic by single inhalation exposures (rat 4 hr LC_{50} >0.5$\leq$5.0 mg/l). Where systemic toxicity was found, all these compounds caused cyanosis and increased respiratory rate from methemoglobinemia. No further testing is proposed on acute toxicity.

Mammalian Repeated Dose Toxicity

Oral or inhalation repeated exposure studies have been completed on two of the four compounds, N,N-diethyl aniline and N-ethyl-m-toluidine. Repeated exposure studies have also been completed on related aromatic amines: aniline, N,N-dimethyl aniline, o-toluidine, m-toluidine, and p-toluidine. Regardless of exposure route or length, all of these aromatic amines affected the blood as the primary target organ. The blood effects included methemoglobinemia, hemolytic anemia, splenomegaly, extramedullary hematopoiesis, reticulocytosis, Heinz bodies, and hemosiderosis. In a direct comparison, aniline and o-toluidine were given orally to rats for 5, 10, or 20 days at ¼ of the LD_{50}. Histopathology examinations found splenic congestion, increased hematopoiesis, hemosiderosis, and bone marrow hyperplasia from both chemicals (Short et al, 1983). Rats were exposed to aniline by inhalation for 10 days over a 14 day period, followed by a two week recovery period. Hematological parameters were affected, and the organ to body weight ratios for the liver, spleen, and thymus were increased (O'Neal et al, 1982). A directly comparable inhalation study of N-ethyl-m-toluidine found similar hematological effects. Changes in the liver, spleen, bone marrow, and kidneys were secondary to effects on the blood (Stephens et al, 1999). A 30 day gavage study of m-toluidine and a 28 day gavage study of N,N-diethyl aniline in rats also found hematological effects and no other target organs. A 14 day gavage study in rats and a 15 day study in mice of N,N-dimethyl aniline found similar effects on the blood. A 28 day dietary study of p-toluidine in rats at rather low doses found decreased body weight gains and increased liver weight; no hematology data were given. Thus, in all eight of these screening studies of four weeks of exposure or less where hematology results were reported, pathological changes were found only in the blood and in other organs affected by the blood changes. Based on the consistency of these effects, as well as the acute results for all the compounds, N-ethyl aniline, N,N-dimethyl-p-toluidine, and N-ethyl-m-toluidine are proposed to be covered by the results of the other monocyclic aromatic amines, and no further repeated exposure testing is proposed.

Genetic Toxicity

Standard bacterial mutagenicity assays with and without metabolic activation have been conducted for all four HPV compounds. Only N-ethyl-m-toluidine was positive, with metabolic activation.

Two of the four compounds have been tested for clastogenicity, and there is information on related aromatic amines. N,N-Dimethyl-p-toluidine induced chromosome aberrations *in vitro* in Chinese hamster V79 (fibroblast) cells without activation, while N,N-diethylaniline did not induce micronuclei in the mouse micronucleus assay. N-Ethyl aniline and N-ethyl-m-toluidine have not been tested for clastogenicity. A number of assays have been done on related aromatic amines in this category. N,N-dimethyl aniline induced chromosome aberrations *in vitro* in Chinese hamster ovary and V79 cells. Aniline caused chromosome aberrations *in vitro* in Chinese hamster ovary and lung cells with activation, and in Chinese hamster V79 cells both with and without activation. Positive and negative results occurred in mouse and rat micronucleus assays with aniline, but most were positive. However, aniline did not cause a dominant lethal effect in rats. p-Toluidine also induced chromosome aberrations in Chinese hamster lung cells with activation, but it did not increase micronuclei in the mouse micronucleus assay. o-Toluidine caused chromosome aberrations in most assays *in vitro,* including in rat liver and Chinese hamster liver, lung, and ovary cells, but not *in vivo* in most of the micronucleus assays (Danford, 1991). A long treatment time was needed *in vitro* for a positive result.

The low pH SHE cell transformation assay has been found to be a useful short-term test for the identification of rodent carcinogens. The use of a lower pH has resulted in demonstration of a dose-response relationship for carcinogens, which was difficult to do with the earlier protocol in SHE cells (Yamasaki, 1996). A recent study found that there was excellent correlation between this assay and long-term rodent studies for a group of 10 aromatic amines and nitroaromatics (Kerckaert et al, 1998). The assay outperformed the Ames test in specificity, correctly identifying chemicals that were positive in the Ames test but not rodent carcinogens. o-Toluidine was one of the chemicals tested in this study, and it was found to cause cell transformation. o-Toluidine was also positive in SHE cells and many other cell lines at neutral pH.

Aniline has not been tested using the low pH protocol, but it was also tested in several cell lines at neutral pH. While most of these older assays were negative, a few were reported to be positive. Based on the usefulness of this assay for aromatic amines, the Panel proposes to do low pH cell transformation assays on N-ethyl aniline and N-ethyl-m-toluidine.

Developmental and Reproductive Toxicity

Screening developmental toxicity studies in mice for N,N-diethylaniline categorized this compound as a low priority for further study. A full developmental toxicity study in rats for N,N-diethyl aniline found fetotoxicity at maternally toxic doses, but no evidence of teratogenicity or embryotoxicity. Other compounds in the category have also been tested for developmental toxicity. A mouse screening developmental toxicity study of N,N-dimethyl aniline also placed it as a low priority for additional studies. A full developmental toxicity study of aniline failed to find evidence of a teratogenic effect. When methemoglobinemia is induced in the gravid female by these aromatic amines, the fetus is also adversely affected by lack of oxygen. There is no evidence of increased susceptibility of the fetus in these developmental studies, however. The repeated dosing studies discussed above for this category show that studies in rodents with exposure duration similar to that of a developmental toxicity study will cause the adverse effects described on the blood. Based on these results, N-ethyl aniline, N-ethyl-m-toluidine, and N,N-dimethyl-p-toluidine are covered by the testing of the related compounds, and no developmental toxicity testing is proposed.

Consideration is given to effects on reproductive organs in repeated exposure studies to determine whether reproductive toxicity studies are needed. The four week oral study of N,N-diethyl aniline in rats did not find any evidence of pathology in the reproductive organs, nor did the two week inhalation study of N-ethyl-m-toluidine in rats. All of the related chemicals in this category have undergone long-term animal studies. Subchronic and chronic studies of N,N-dimethyl aniline, o-toluidine, and aniline in rats and mice found no evidence that reproductive function would be affected, nor did 78 week studies of m-toluidine and p-toluidine in rats. A dominant lethal study of aniline in rats was also completed to address the possibility of heritable effects being transmitted to the offspring from parental males. No dominant lethal effect was found in the rat. In keeping with the lack of heritable genetic damage from aniline exposure, o-toluidine did not cause sperm-head abnormalities in mice. o-Toluidine was also tested for reproductive effects in a dermal screen in which mice were treated for four months before mating and offspring were maintained up to two months of age. While there was evidence of systemic toxicity, there were no effects on fertility or signs of embryotoxicity, and no evidence of greater sensitivity of the reproductive system as compared to general toxicity. No reproductive toxicity testing has been completed for N,N-diethyl aniline, N-ethyl-m-toluidine, N-ethyl aniline, and N,N-dimethyl-p-toluidine. These chemicals are covered by the subchronic, chronic, and developmental data discussed above for these and related aromatic amines, and no further testing for reproductive toxicity is proposed.

The existing data and proposed test plan are summarized in Table 2 below.

Table 2. Summary of Data Gaps and Method of Completion

	Aniline 62-53-3	o-Toluidine 95-53-4	p-Toluidine 106-49-0	m-Toluidine 108-44-1	N,N-Dimethyl aniline 121-69-7	N-ethyl aniline 103-69-5	N,N-dimethyl-p-toluidine 99-97-8	N-Ethyl-m-Toluidine 102-27-2	N,N-Diethyl aniline 91-66-7
Environmental Fate									
Photodegradation	A	S	S	S	A	S	S	S	S
Hydrolysis	A	A	A		A	C	C	C	C
Fugacity	S	S	S	S	S	S	S	S	A
Biodegradation	A	A	A	A	A	A	C	A	A
Eco Toxicity									
Acute fish	A	A	A	A	A	A	A	A	A
Acute invertebrate	A	A	A	A	A	A	A	S	A
Acute algal	A	A	A	A	A	A	S	S	A
Mammalian Toxicity									
Acute toxicity	A	A	A	A	A	A	A	A	A
Repeated dose toxicity	A	A	A	A	A	C	C	C; NG	A
Genetic toxicity									
in vitro: gene mutation	A	A	A	A	A	A	A	A	A
in vitro: chromosome aberrations	A	A	A		A		A		
in vitro: cell transformation (SHE cells)	A	A				T		T	
in vivo: chromosome aberrations	A	A	A						A
Reproductive toxicity	P	P; NG	P	P	P	C	C	C	C
Developmental toxicity	A	NG			NG	C	C	C	A; NG

= ICCA and OECD SIDS chemicals (testing will be addressed under ICCA HPV Program)

A = Adequate data available
NG=Non-guideline data available
C = Use of Category Approach
T = Testing to be done
S = Structure-activity relationship (modeling program used)
P = ≥90 Day study found no pathology of reproductive organs

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